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AMENDMENTS

IN THE SPECIFICATION

On page 6, please delete paragraph **[0021]** and replace it with the following paragraph:

[0021] The invention includes a composition and method of treatment of sinusitis. A preferred embodiment of the invention is composition for the treatment of sinusitis comprising a therapeutically effective amount of one or more peptides selected from the group of peptides with a C-terminal sequence consisting of KPV (**SEQ ID NO:1**), HFRWGKPV (**SEQ ID NO:2**), and SYSMEHFRWGKPV (**SEQ ID NO:3**) in combination with a therapeutically effective amount of a antihistamine/decongestant.

A1

On page 6, please delete paragraph **[0025]** and replace it with the following paragraph:

[0025] More preferably still, the peptides in each of these preferred combination compositions has the primary sequence of KPV (**SEQ ID NO:1**) or VPK-Ac-CC-Ac-KPV (Ac=Acetyl group). In all the preferred compositions, pharmacologically effective concentrations of the peptides may be as low as 10^{-12}M but may be as high 10^{-4} M.

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On page 7, please delete paragraph **[0026]** and replace it with the following paragraph:

[0026] In another embodiment of the invention a peptide of one or more peptides selected from the group of peptides with a C-terminal sequence consisting of KPV (**SEQ ID NO:1**), HFRWGKPV (**SEQ ID NO:2**), and SYSMEHFRWGKPV (**SEQ ID NO:3**) is topically or systemically applied to treat sinusitis.

A3

On page 7, please delete paragraph **[0028]** and replace it with the following paragraph:

[0028] In yet another embodiment of the invention, one or one or more peptides selected from the group of peptides with a C-terminal sequence consisting of KPV (**SEQ ID NO:1**), HFRWGKPV (**SEQ ID NO:2**), and SYSMEHFRWGKPV (**SEQ ID NO:3**), which may or may not be in combination with therapeutically effective amounts of antibiotics, corticosteroids, fungicides and/or antihistamine/decongestants, are topically or systemically applied before, during or after surgery to treat sinusitis.

A4

On page 11, please delete paragraph **[0056]** and replace it with the following paragraph:

[0056] Figure 25 illustrates the anti-inflammatory effects of the KPV (**SEQ ID NO:1**) peptide, KPV dimer and prednisolone on edema induced in the hind paw of mice by the injection α-carageenan as a function of time.

A5

On page 11, please delete paragraph **[0057]** and replace it with the following paragraph:

[0057] The references cited below are hereby incorporated by reference as if fully set forth herein. α-MSH is a 13 amino acid, anti-inflammatory, anti-fugal peptide with the primary sequence SYSMEHFRWGKPV (**SEQ ID NO:3**). In addition to its anti-fungal, anti-inflammatory properties, it also has anti-pyretic properties. The C-terminal trimer, KPV (**SEQ ID NO:1**), appears responsible for these properties. Lipton, J.M., Antipyretic and Anti-inflammatory Lys-Pro-Val- Compositions and Methods of Use, U.S. Patent No. 5,028,592, issued July 2, 1991; Lipton, J.M., Antipyretic and Anti-inflammatory Lys-Pro-Val- Compositions and Methods of Use, U.S. Patent No. 5,157,023, issued October 20, 1992; Catania, A., Lipton J.M., α-Melanocyte Stimulating Hormone in the Modulation of Host Reactions, 14 *Endocr. Rev.*, 564-576 (1993); Lipton, J. M., Catania, A., Anti-

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A6 CONT.

inflammatory Influence of the Neuroimmunomodulator α–MSH, 18 *Immunol. Today*, 140-145 (1997).

On page 13, please delete paragraph **[0061]** and replace it with the following paragraph:

A7

[0061] The broadest aspect of the invention is a composition and method of treatment of pathologies of the facial and maxillary sinuses having an inflammatory and/or fungal component. A preferred embodiment of the invention is composition for the treatment of sinusitis comprising a therapeutically effective amount of one or more peptides selected from the group of peptides with a C-terminal sequence consisting of KPV (**SEQ ID NO:1**), HFRWGKPV (**SEQ ID NO:2**), and SYSMEHFRWGKPV (**SEQ ID NO:3**) in combination with a therapeutically effective amount of an antihistamine/decongestant selected from the group consisting of: pseudoephidrine, phenylephrine, phenylpropanolamine, chloropheniramine, bromopheniramine, pheniramine and loratidine.

On page 13, please delete paragraph **[0062]** and replace it with the following paragraph:

[0062] Another preferred embodiment of the invention is a composition for the treatment of sinusitis comprising a therapeutically effective amount of one or more peptides selected from the group of peptides with a C-terminal sequence consisting of KPV (**SEQ ID NO:1**), HFRWGKPV (**SEQ ID NO:2**), and SYSMEHFRWGKPV (**SEQ ID NO:3**) in combination with a therapeutically effective amount of a corticosteroid selected from the group consisting of: betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisone, prednisone, and triamcinolone.

On page 14, please delete paragraph **[0065]** and replace it with the following paragraph:

A8

[0065] More preferably still, the peptides in each of these preferred combination compositions has the primary sequence of KPV (**SEQ ID NO:1**) or VPK-Ac-CC-Ac-KPV (Ac=Acetyl group). In all the preferred compositions, pharmacologically effective concentrations of the peptides may be as low as 10^{-12}M but may be as high 10^{-4} M.

On page 14, please delete paragraph **[0066]** and replace it with the following paragraph:

[0066] In yet another embodiment of the invention, one or one or more peptides selected from the group of peptides with a C-terminal sequence consisting of KPV (**SEQ ID NO:1**), HFRWGKPV (**SEQ ID NO:2**), and SYSMEHFRWGKPV (**SEQ ID NO:3**), which may or may not be in combination with therapeutically effective amounts of antibiotics, corticosteroids, fungicides and/or antihistamine/decongestants is dissolved in a carrier. Formulations for solution or solids based drug delivery carriers are well known in the art. Such preferred carriers may be selected from the group consisting of saline, phosphate buffered saline, gelatin, maltodextrin, cellulose, microcrystalline cellulose, methyl cellulose and carboxymethyl cellulose.

On page 15, please delete paragraph **[0068]** and replace it with the following paragraph:

A9

[0068] Another embodiment of the invention is a method for the treatment of sinusitis comprising topical or systemic administration of one or more peptides selected from the group of peptides with a C-terminal sequence consisting of KPV (**SEQ ID NO:1**), HFRWGKPV (**SEQ ID NO:2**), and SYSMEHFRWGKPV (**SEQ ID NO:3**). In another preferred method of the invention, one or more of these preferred peptides used in

combination with therapeutically effective amounts of antihistamines/decongestants, corticosteroids, antibiotics, and/or fungicides, are topically or systemically applied to treat sinusitis.

A9 cont.

On page 15, please delete paragraph **[0069]** and replace it with the following paragraph:

[0069] In yet another embodiment of the invention, one or one or more peptides selected from the group of peptides with a C-terminal sequence consisting of KPV (**SEQ ID NO:1**), HFRWGKPV (**SEQ ID NO:2**), and SYSMEHFRWGKPV (**SEQ ID NO:3**), which may or may not be in combination with therapeutically effective amounts of antibiotics, corticosteroids, fungicides and/or antihistamine/decongestants, are topically or systemically applied before, during or after surgery to treat sinusitis.

On page 16, please delete paragraph **[0071]** and replace it with the following paragraph:

A10

[0071] The peptides used in the following examples include: α-MSH (1-13), (4-10), (6-13), and (11-13), all of which were N-acetylated and C-amidated, and ACTH (1-39) and (18-39) (CLIP). These peptides were prepared by solid-phase peptide synthesis and purified by reversed phased high performance liquid chromatography. Some examples also include a dimer of the amino acid sequence KPV (**SEQ ID NO:1**), VPK-Ac-CC-Ac-KPV, which also was N-acetylated and C-amidated (KPV dimer). Dimers can be formed by adding cysteines at the N-termini of any of the above polypeptides and allowing the cysteines of two polypeptides to form a disulfide bond. Both homo-dimers and hetero-dimers can be formed using this method.

On page 18, please delete paragraph **[0079]** and replace it with the following paragraph:

[0079] These results show that α–MSH(1-13), its C-terminal tripeptide (11-13), and other α–MSH fragments have significant fungicidal effects against *C. albicans*. The most effective of the α–MSH peptides were those including the C-terminal amino acid sequence KPV (**SEQ ID NO:1**) of the α–MHS sequence, i.e., α–MSH (1-13), (6-13) and (11-13). In addition, the sequence VPK-Ac-CC-Ac-KPV has also been shown to be at least as effective as α–MSH (11-13) against microbes. The α–MSH core sequence (4-10), which is known to influence learning and memory, but has little antipyretic and anti-inflammatory influence, was effective, but less so. The ACTH peptides (1-39) and (18-39) did not have significant candidacidal effects. These observations indicate that antifungal activity is not common to all melanocortin peptides, but rather is specific to α–MSH amino acid sequences, and most particularly to the C-terminal amino-acid sequences of α–MSH. This strongly suggests that α–MSH(1-13), its C-terminal tripeptide (11-13), and other α–MSH fragments could server as a basis for a therapeutic treatment of sinusitis having a fungal component.

On page 20, please delete paragraph **[0082]** and replace it with the following paragraph:

[0082] These results show that α-MSH(1-13), α-MSH(6-13), and α-MSH(11-13) all significantly inhibit germination by *C. albicans*. The infection cycle of *C. albicans*, and candida in general, begins with adherence of fungal cells to epithelial cells. After adhesion, the fungal cells undergo a switch from ellipsoid blastophore form to various filamentous forms, including germ tubes, pseudohyphae, and hyphae. Gow, N.A., Germ Tube Growth of Candida Albicans, *Curr. Topics Med. Mycol.* **8**, 43 –45 (1997). α-MSH peptides were added to *C. albicans* after promotion of hyphal growth. α-MSH(1-13)

inhibited subsequent germ tube formation by approximately 30%, α-MSH(11-13) inhibited germ tube formation by approximately 56%, and α-MSH(6-13) inhibited germ tube formation by approximately 50%. As with the results in example 1, the highest level of inhibition is observed for the tripeptide containing only the C-terminal KPV (**SEQ ID NO:1**) amino acid sequence. The results of example 2 suggest that α-MSH(1-13), fragments of α-MSH(1-13), or peptides containing the C-terminal KPV (**SEQ ID NO:1**) amino acid sequence of the α-MSH peptides could be of therapeutic use not only in the prevention and treatment of early fungal infection as stated in example 1, but also in the treatment of later stage fungal infections. By preventing germination, the α-MSH peptides could prevent the innervation of the epithelial cells that occurs during chronic candidiasis, thus providing a tool to combat long-term fungal infection, particularly fungal infection leading to sinusitis. This therapy would be especially beneficial to immunocompromised patients, who tend to exhibit a high rate of candidal infections.

A12 cont.

On page 27, please delete paragraph **[0095]** and replace it with the following paragraph:

A13

[0095] These results show that a peptide containing the KPV (**SEQ ID NO:1**) amino acid sequence of α-MSH has anti-inflammatory properties. Rabbits injected with histamine after injection of a blue marking dye will exhibit blue weal formation around the injection site. This occurs because histamine increases blood vessel permeability, allowing the dye to seep into the injection area. When the rabbits were pre-injected with as little as 1.25 μg/kg body weight of a protected KPV (**SEQ ID NO:1**) tripeptide, the histamine-induced weal exhibited a substantially less intense blue color. This suggests that the KPV (**SEQ ID NO:1**) tripeptide is interfering with the ability of histamine to increase blood vessel

permeability. Histamine plays a central role in the inflammation reaction by dilating blood vessels, increasing vessel permeability, and increasing blood flow. Histamine also triggers the release of cytokines by leukocytes, which further increases the inflammation reaction. The ability of the KPV (**SEQ ID NO:1**) tripeptide to block histamine function suggests that peptides containing the α-MSH KPV (**SEQ ID NO:1**) amino acid sequence could serve as potent anti-inflammatory agents.

A13 cont.

On page 28, please delete paragraph **[0099]** and replace it with the following paragraph:

A14

[0099] These results show that a peptide containing the KPV (**SEQ ID NO:1**) amino acid sequence of α-MSH could serve as a potential replacement for corticosteroids in the treatment of inflammation. α-MSH(11-13) was compared to hydrocortisone for its ability to prevent carrageenan-induced rat paw inflammation. The development of swelling after carrageenan injection is a biphasic event. The first phase, occurring approximately 1 hour after injection, is attributed to the release of histamine and serotonin. The second phase is attributed to the release of prostaglandin-like substances, and is sensitive to both steroidal and non-steroidal anti-inflammatory agents. Prostaglandins are produced from arachidonic acid by cyclooxygenase, and like histamine they serve to increase blood vessel permeability. During the first hour after carrageenan injections, hydrocortisone caused approximately a 30% decrease in paw inflammation, while no such reduction was observed in the presence of α-MSH(11-13). Between 1 and 4 hours, however, α-MSH(11-13) and hydrocortisone exhibited nearly identical anti-inflammatory activity. Corticosteroids such as hydrocortisone inhibit inflammation by preventing the release of arachidonic acid from phospholipids, which in

turn inhibits the formation of prostaglandins. While example 5 suggested that the α-MSH tripeptide inhibits inflammation by blocking histamine function, example 6 suggests that α-MSH may also inhibit inflammation via a mechanism similar to that of the corticosteroids. It is also believed that α-MSH serves to inhibit inflammation by increasing the formation of endogenous corticosteroids. These substances are up-regulated by ACTH, which like α-MSH is a melanocortin peptide. Regardless of the exact mechanism of α-MSH anti-inflammatory activity, these results suggest that peptides containing the C-terminal α-MSH amino acid sequence KPV (**SEQ ID NO:1**) have potential therapeutic utility in the treatment of inflammation, particularly inflammation tied to sinusitis.

A14 CONT.

On page 46, please delete paragraph **[0134]** and replace it with the following paragraph:

A15

[0134] Experiment 10 suggests that preferred compositions according to the invention are comparable to prednisolone for reducing inflammation and accordingly, may serve as therapeutic replacement of prednisolone for the treatement of sinusitis. Experiment 10 compares the anti-inflammatory effects of KPV (**SEQ ID NO:1**) and the KPV dimer (referred to as $(CKPV)_2$) in reducing edema in the hind paw of male ICR CD-1 mice injected with λ-Carrageenan. A total of 162 male ICR CD-1 mice were used in three different experiments. Each mouse received a single subcutaneous injection (20 µl) of a carrageenan solution (0,125 % in saline) in each hind paw to induce edema. Paw volume thickness was measured with a micrometer. In order to compare the anti-inflammatory effectiveness of the peptides according to the invention relative to prednisolone, the 162 mice were divided into 10 groups where each group received the following 200 µl

dosages (the number of animals is shown in parenthesis: Saline control (31), $(CKPV)_2$ 0,5 mg/Kg (7), $(CKPV)_2$ 1,25 mg/Kg (7), $(CKPV)_2$ 2,5 mg/Kg (16), $(CKPV)_2$ 5,0 mg/Kg (17), $(CKPV)_2$ 7,5 mg/Kg (17), KPV (**SEQ ID NO:1**) 2,5 mg/Kg (9), KPV (**SEQ ID NO:1**) 5,0 mg/Kg (17), KPV (**SEQ ID NO:1**) 7,5 mg/Kg (24) and prednisolone suc. 100 mg/Kg (17). The experiment was run for three hours and paw pad thickness was measured at 1.5 hr and 3hr following injection of the anti-inflammatory agents. The results of this experiment are shown in Figure 26. Figure 26 shows that dosages of $(CKPV)_2$ at 1.25 mg/Kg, 2.5 mg/Kg, 5.0 mg/Kg, and 7.5 mg/Kg and the dosage of KPV (**SEQ ID NO:1**) at 5.00 mg/Kg, each reduced paw edema by approximately 15-30% versus the approximate 50% reduction in paw edema by prednisolone. Although this experiment suggests that prednisolone is more effective at reducing inflammation than the peptides according to the invention, as taught in the earlier sections, the peptides according to the invention reduce inflammation without the immuno-suppresive and other deleterious side-effects of steroidal anti-inflammatories such as prednisolone.

A15 Cont.